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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,045	12/07/2000	Andrew Paul Chapman	CARP-0086	3379

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,045	CHAPMAN ET AL.	
	Examiner	Art Unit	
	David A. Saunders, PhD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 25 April 2005.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-10,12-15 is/are rejected.

7)☒ Claim(s) 11 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/25/05 has been entered.

Claims 1-15 are pending and under examination. Claims 8-9 have been rejoined.

The disclosure is objected to because of the following informalities: At page 6, line 2 "bridie" should be - - bridge - -.

Appropriate correction is required.

The 112, second paragraph rejection of record (action mailed 3/24/04) has been withdrawn.

The 112, first paragraph rejection of record (action of 3/24/0/4, pages 2-3 has been withdrawn. It is noted that claim 1 requires that the non-disulfide bridge be linked to "the sulfur atom of a cysteine residue" in each of the heavy chains - - i.e. the linking of the bridge is "site – specific". It is noted that the pharmacokinetics of a site-specific DFM-PEG 40K Da conjugate are compared against DFM in Figure 2 and in Table 2, with the former showing improved pharmacokinetics compared to the latter.

Likewise, Figure 9 and Table 6 compare the pharmacokinetics of a site-specific DFM – PEG 40K Da conjugate against a DFM, with the former showing improved pharmacokinetics compared to the latter.

Thus the comparisions in the disclosure compare the pharmacokinetics of a divalent antibody, with or without a site – specific conjugated polymer, rather than the pharmacokinetics of a divalent antibody with site-specific or ramdomly conjugated polymer. Claim 1 as recited thus has no new matter.

To clarify the record it is to be noted that, contrary to applicant's urgings (page 9), Tables 2 and 6 do specify that the linkage of the polymer is site-specific, since these Tables are derived from data in Figs. 2 and 9, for which the linkage, of the DFM – PEG 40K Da is described as "site – specific". See page 14, line 34 and page 15, line 24. This difference between applicant's and examiner's interpretation of the Figs. and Tables, however, makes no difference in arriving at the conclusion that claim 1 recites no new matter.

The 112, first paragraph rejection (action of 3/24/04 at pages 3+) has been withdrawn; it is deemed that the essential feature is that there be a polymer serving as an interchain bridge between the sites specified in claim 1, rather than that the particular chemical nature or mw of the polymer be defined.

For like reasons the 112, first para. enablement rejection (page 5) has been withdrawn.

The prior art rejections of record are maintained as follows.

Claims 1-10, 12-13 and 15 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gonzales et al (6,025,158).

Gonzales et al teach antibody fragments having an extended circulating half life by virtue of being conjugated to a high m.w. polymer – e.g. PEG of 20,000 D or greater. Gonzales et al disclose embodiments in which two or more Fab, Fab or Fab'-SH fragments are covalently conjugated to a polymer backbone. The polymer thus links the antibody fragments. See especially col. 35, lines 40-57; wherein there is a teaching of a "polymer molecule used to link together two antibody fragments to form a dumbell – shaped structure." Such a "dumbbell – shaped structure" is consistent with the divalent antibody fragment of instant claim 1.

A preferred site of conjugating the polymer to the antibody fragment is at the bindge region of the latter, a most preferred site of attachment therein is a cysteine residue. See, for example, col. 19, lines 56-65. The conjugation of the polymer thereto is achieved by providing a sulfhydryl reactive moiety attached to PEG. See, for example, col. 19, lines 35-55; col. 42, lines 12-18; col. 120, lines 46-52; col. 121, lines 59-64.

From the above claims 1-2 are anticipated or, at the least, obvious as one of numerous embodiments taught within the four corners of the reference.

Regarding claims 3-4, note the teachings regarding the structure of Fab' and Fab'-SH fragments at col. 11, lines 56-64. The structure of further dependent claim 5 would be achieved when one couples the taught Fab'-SH to two activated sites on a polymer to form the dumbbell structure taught at col. 35, lines 45-57.

Regarding claims 6-9, note the polymers taught at col. 41, lines 1-34. Note PEG taught therein at line 9. Note methoxy PEG and molec. Weight thereof at col. 120, lines 45-52.

Regarding the cross-linkers of instant claim 10, note Gonzales et al at col. 35, lines 53-57 and col. 41, lines 41-43.

With respect to calim 12, note Gonzales et al. teach conjugation of label/ reporter groups at col. 44, line 5-col. 45, line 14.

Regarding claim 13, the IL-8, for which the exemplified antibodies of Gonzales et al are specific, is a soluble antigen, secreted by cells (col. 1, lines 44-45).

For claim 15, note col. 45, lines 22-25.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzales et al in view of Barbanti et al (5,436,154).

Gonzales et al have been noted supra for generically teaching the coupling/bridging of Fab, Fab' or Fab'-SH antibody fragments of generic binding specificity, or more particularly of IL-8 binding specificity, to a polymer to extend circulating half-life.

Gonzales et al clearly teach (col. 16, lines 39-46) that the benefits of entended circulating half-life gained by conjugation to the polymer are to be expected "without regard to antigen specificity" of the antibody.

Barbanti et al teach antibodies to TNF-alpha, including fragments of such antibodies (col. 5, lines 44-55). It would have been obvious to conjugate these antibody fragment of Barbanti et al to PEG in the manner taught by Gonzales et al, in order to

also extend half life of the antibodies. One of skill would have been reasonably motivated to consider both references, because both IL-8 and TNF-alpha are involved in inflammation and because increasing the circulating half life of an antibody to any mediator of inflammation would have been expected to permit more of the administered antibody to bind the mediator.

The above restatement of the rejection of record action of 3/24/04) has more specifically pointed out the portions of Gonzales et al that are relevant to the claimed invention. Applicant's urgings filed on 4/25/05 thus do not need to be addressed in a detailed manner, however the examiner makes the following brief comments.

At pages 12-13, applicant refers to a teaching by Gonzales et al at col. 23, line 7 – col. 25, line 44 and col. 31, line 55 – col. 34, line 28, wherein the corpling of F(ab')2 to PEG is described. The examiner has not relied upon such teaching and has noted supra where Gonzales et al teach conjugation of F(ab') – SH fragments are attached to a polymer to form a "dumbell" (col. 35, line 47); the resulting structure would be divalent as claimed. Examiner further notes that applicant has exemplified the coupling of Fab' fragments to the polymer.

At page 13 applicant has also urged that Gonzales et al teach PEG attachment to lysines using N-hydroxy – succinamide chemistry. The examiner has noted supra where Gonzales et al teach compling to a cysteine, within the hinge region via maleimide chemistry.

Also at page 13, applicant has picked out passages where Gonzales et al do not specify where on the antibody fragments the polymer is to be attached. The examiner

has pointed out supra those passages, out of many that point to attachment to a cysteine residue within the hinge region.

Applicant has urged (page 14) that where the examiner relies upon teachings of coupling Fab' or Fab' – SH fragments, the examiner is relying upon a teaching of monovalent fragments, whereas the claim calls for divatent fragments. Examiner notes that when two Fab' or Fab'-SH fragments are attached to form a dumbbell that a divalent fragement results, as claimed. Furthermore applicant's own examples show cnstructs designated as "DFM-DEG" in which "two Fab' fragments are cross linked" (see page 15, lines 30-32 and all examples). Applicant cannot therefore argue that the examiner was in error to rely respone the teachings of Gonzales et al that pertain to the conjugation of Fab' or Fab' – SH.

Applicant's urgings regarding the 103 rejection over Gonzales et al in view of Barbanti et al merely respect the erroneous arguments concerning the teachings of Gonzales et al. Applicant has urged Barbanti et al teach whole antibodies, not fragments; examiner notes that fragments are clearly encompassed within the four corners of the reference - - e.g. col. 3, lines 48-50; col. 5, lines 44-55. Otherwise applicant has argued the Barbanti et al reference in isolation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Saunders whose telephone number is (571) 272-0849. The examiner can normally be reached on Monday to Thursday from 8 AM to 5:30 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A Saunders

Saunders/LR
June 24, 2005

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~162~~ 1644